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Prognosis of 1,169 hepatitis C chronically-infected patients with decompensated cirrhosis in the pre-direct acting antiviral era

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SUMMARY

At a population level, little is known regarding the risk of liver- and non-liver-related mortality and hospitalization and the development of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV) infected patients with decompensated cirrhosis (DC). This large-scale national record-linkage study estimates these outcomes following first hospital admission for DC. Record-linkages between national HCV diagnosis and clinical databases and the national inpatient hospital episode database and mortality register were conducted to follow up the disease course of all identified HCV-diagnosed and chronically-infected persons. The study population consisted of 1,169 HCV chronically-infected persons who had a first hospital admission for DC within the period 1994–2013. We observed an overall average annual percentage change of 12.6% in new DC patients (from 63 in 1994-1999 to 541 in 2009-2013), with no evidence for any improvement in the relative risks of liver-related or all-cause death over time. Between 1 January 1994 and 31 May 2014, 722 and 95 DC patients had died of a liver- and a non-liver related cause, respectively, and 106 patients had a subsequent first admission for HCC. The five-year cumulative incidence of liver-related mortality, non-liver related mortality, and first subsequent HCC admission was 61.3%, 8.2%, and 8.8%, respectively. The health burden in HCV-infected patients associated with development of decompensated cirrhosis has increased dramatically over the last 20 years. Our findings establish the baseline mortality and HCC progression rates in DC patients against which the impact of new antiviral therapies can be measured.

Keywords Decompensated cirrhosis; hepatocellular carcinoma; mortality; Scotland; record-linkage

INTRODUCTION

One of the most severe sequelae of chronic infection with the hepatitis C virus (HCV) is decompensated cirrhosis (DC), which refers to clinical progression following the generally asymptomatic compensated phase of cirrhosis. Complications comprising DC include jaundice, variceal haemorrhage, ascites, and encephalopathy. An estimated 30% of patients with cirrhosis progress to DC within 10 years (1), with an estimated annual risk of 3–6% (1, 2). Mortality following DC without liver transplantation is very high – the annual mortality risk has been estimated in the range of 12–14% from small studies of HCV-infected patients (1, 2, 3).

Historically, HCV-infected patients with decompensated liver disease have not been recommended for interferon-based treatment, due to a greater impact of adverse effects and a lower chance of successful viral clearance compared with treatment at the compensated stage of cirrhosis (4, 5). New interferon-free therapies with better tolerability, greater safety and simplified monitoring protocols promise improved treatment options for those with severe liver disease (6-8). Importantly, to assess the clinical value of these new therapies we need to have a thorough understanding of the extent of mortality and morbidity among DC patients.

A national record-linkage study conducted previously in Scotland for the period 1991-2005 reported an average annual increase of 10.7% in the number of new presentations with HCV-related DC (9). The risk of developing DC in this population was found to be associated with epidemiological characteristics including older age, a history of problem alcohol use, and HIV co-infection. Outcomes following DC were not investigated; in the current study, we expand upon this earlier research by setting this rising trend in the annual number of DC cases in context of the disease burden experienced by these patients.

Therefore, the principal purpose of this study is to further our understanding of the natural history of HCV-related DC during the pre-DAA (direct-acting antivirals) era, so that we can assess the impact of highly effective DAA regimens – now being introduced – on the risk of death from liver failure and the development of such complications as hepatocellular carcinoma (HCC). These findings will constitute a historical baseline against which future outcomes can be gauged. In the current study, we describe the frequency of liver-related and all-cause mortality and first-time hospital admissions for HCC among Scotland's HCV-infected DC patient population, and report the risk of mortality and associated patient factors.

MATERIALS AND METHODS

Design

The design was a retrospective cohort study, using record-linkage between national databases to determine the health burden among HCV chronically-infected persons who have reached the DC stage of liver disease.

Data sources

Health Protection Scotland maintains the HCV Diagnosis database, which is a database of all persons who have been diagnosed HCV positive in Scotland since testing began in 1991 (including stored serum back to 1985)(10). Laboratory detection of hepatitis C antibody positivity is a requirement for inclusion. This database contains the following limited non-named information: surname Soundex (a consonant-only phonetic encoding), forename initial, date of birth, sex, and postcode district of residence, as well as data concerning risk activities for acquiring infection. As of 31 December 2013, this database contained records for 35,474 individuals (11), while an

estimated 55% of the current HCV infected Scottish population have been diagnosed (12).

The Scottish Hepatitis C Clinical database, also held at Health Protection Scotland, consists of data on all aspects of HCV care and patient management, installed across specialist HCV treatment centres in Scotland (see Ref. (13), for further details).

Hospital admission data form the Scottish Morbidity Records, an episode-based patient record held by Information Services Division (a division of NHS National Services Scotland) of all general acute inpatient and day-case hospital discharges. Discharge diagnoses use International Classification of Diseases (ICD) Ninth Revision for discharges in the period 1989-1995, and the Tenth Revision for discharges between 1996 and 2014.

Mortality data was provided by death registrations held by the National Records of Scotland (NRS), formerly the General Register Office for Scotland (GROS). Underlying and contributing causes of death are coded, as for the Scottish Morbidity Records, using the ICD Ninth Revision for deaths occurring in the period 1989-1995, and the Tenth Revision for deaths in 1996-2014.

Record linkage

Linkage of records between the HCV Diagnosis database and the Scottish Morbidity Records and death registrations was carried out by Information Services Division using probabilistic record-linkage techniques (14); this methodology allows for matches using incomplete identifiers. The linked dataset was anonymized before transfer to HPS for analysis. Linkage between the HCV Diagnosis database and the Scottish Hepatitis C Clinical database was also conducted, to determine the HCV RNA status at baseline for those DC patients treated with antiviral therapy

(see Ref. (15) for further details). Linkages were approved by the Privacy Advisory Committee, which oversees confidentiality issues involving data held on NHS Scotland patients.

Data analysis

Study population

The study population consisted of all HCV chronically-infected patients with diagnosed DC (defined as first inpatient/day-case hospital episode with a relevant ICD-9 or ICD-10 code in either the main or five supplementary diagnosis fields of the episode record) in Scotland over the period 1994-2013, thus providing a 20-year study period. Individuals for whom their first DC hospital admission occurred >1 year before their HCV diagnosis were excluded, to reduce potential bias due to DC resulting from another aetiology. For the restriction to chronic infection, HCV RNA status for each DC patient was determined according to PCR test results (undertaken at the time of the initial HCV diagnosis, or otherwise post-completion of antiviral therapy) held on the HCV Diagnosis and Scottish Hepatitis C Clinical databases; all patients who had changed status from RNA-positive to RNA-negative as a result of successful antiviral therapy either before first DC admission (n=17) or at any time during follow-up (n=36) were also excluded.

The DC codeset consisted of ascites (ICD-10 R18; ICD-9 789.5), bleeding oesophageal varices (ICD-10 I85.0, I98.2, I98.3; ICD-9 456.0), chronic hepatic failure, including hepatic encephalopathy (ICD-10 K72.1, K72.9; ICD-9 572.2, 572.8), alcoholic hepatic failure (K70.4), and hepatorenal syndrome (ICD-10 K76.7; ICD-9 572.4). These codes were common among those used in previous DC research (9, 16), and were selected in consultation with clinicians and epidemiologists working in the field of HCV infection.

Outcome measures and covariates

We report three principal endpoints: liver-related mortality, all-cause mortality, and first HCC admission subsequent to first DC admission, based on the occurrence of a pre-defined set of ICD codes in either the underlying or contributing cause of death fields (mortality) or either the main or supplementary discharge diagnosis fields (hospital admissions). For the liver-related mortality endpoint, the set of ICD codes comprised alcoholic liver disease (ICD-10 K70; ICD-9 571.0–571.3), liver cancer (ICD-10 C22; ICD-9 155), non-alcoholic liver disease (ICD-10 K71–77; ICD-9 570, 571.4–571.9, 572–573), viral hepatitis (ICD-10 B15–19; ICD-9 070), and sequelae of viral hepatitis (ICD-10 B94.2, R17, R18, I85.0, I98.2, I98.3; ICD-9 789.5, 456.0) (17). For the endpoint first HCC admission, the codeset consisted of C22.0 and 155.0. Non-liver related mortality as an additional endpoint was also investigated.

The covariates investigated consisted of: sex, five-year period of first DC admission (1994-1998, 1999-2003, 2004-2008, 2009-2013), first alcohol-related hospital admission, risk group for HCV acquisition (people who inject drugs (PWID), non-PWID, not known), HIV co-infection, and primary DC discharge diagnosis code category. The binary indicator variable HIV co-infected status was determined by searching all linked hospitalization records for each patient; if an HIV code (defined as ICD-10 B20-24; ICD-9 042, V08) occurred in any episode, then the indicator variable was set to one. The three DC discharge diagnosis categories are *hepatic failure* (aggregating the diagnosis codes comprising chronic hepatic failure, alcoholic hepatic failure, and hepatorenal syndrome), *ascites*, and *bleeding varices* (see above). We use the terms admission and discharge equivalently, assuming that discharge diagnoses encode the reason(s) for admission.

Four time-dependent covariates were also included: (i) current age (< 40, 40–49, 50–59, and 60+

years) captures changing membership of 10-year age groups throughout the study period; (ii) date of first HCC hospital admission, if this occurred; (iii) date of first hospital admission with a post-liver transplant diagnosis code, if this occurred ('liver transplant status': ICD-10 Z94.4; ICD-9 V42.7); this served to indicate a recent liver transplantation.

The fourth time-dependent covariate, (iv) first alcohol-related hospital admission, served as a proxy for a history of problem alcohol use. For each DC patient, the occurrence of one or more alcohol-related episodes in their hospitalization history was coded using an indicator variable. This involved searching the linked hospitalization records for alcohol-related discharge diagnosis codes in either the main or a supplementary diagnosis field. The alcohol-related diagnosis codeset consisted of alcohol use (ICD-10 Z72.1), mental and behavioural disorders due to use of alcohol (ICD-10 F10; ICD-9: 291, 303, 305), degeneration of nervous system due to alcohol (ICD-10 G31.2, G62.1, G72.1, I42.6, K29.2; ICD-9 357.5, 425.5, 535.3), toxic effects of alcohol (ICD-10 T51.0, T51.9; ICD-9 980.0), alcoholic liver disease (ICD-10 K70.1-3, K70.9; ICD-9 571.0-571.3), alcohol-induced chronic pancreatitis (ICD-10 K86.0), evidence of alcohol involvement (ICD-10 Y90-1), finding of alcohol in blood (ICD-10 R78.0; ICD-9 790.3), alcohol rehabilitation (ICD-10 Z50.2), and accidental or intentional self-poisoning by and exposure to alcohol (ICD-10 X45, X65; ICD-9 E860.0, E860.9).

Statistical analyses

The average annual percentage change in the number of new DC patients, both overall and stratified by covariate level, was calculated by fitting Poisson regression models to the annual observed numbers over the period 1994–2013. Cumulative incidence plots, per outcome, were produced using a multistate modelling/competing risks approach (18). Transition probabilities between disease states were estimated using the same multistate model; we report annual values

by averaging over the estimated probabilities for each of the first three years of follow-up.

Follow-up time

We used standard person-time methodology. For each endpoint investigated, the follow-up period was defined to begin at the date of the first hospital admission with mention of DC, and to end at the earliest of the date the endpoint occurred or the right-censoring date (31 May 2014). Follow-up was also censored at date of death from a non-liver related cause or from any cause in the analyses of the endpoints liver-related mortality and first HCC admission, respectively.

Cox regression analyses were carried out to estimate the relative risk (as hazard ratios) of all-cause and liver-related mortality associated with the covariates of interest (see above). Violation of the proportional hazards assumption was graphically assessed and additionally tested using Schoenfeld residuals.

Finally, we assessed the presence and impact of potential referral bias that can be present when analysing a prevalent cohort (i.e., the chance of inclusion in the study population may be associated with the outcome(s) of interest; this may be the case for patients who died of DC that had been first diagnosed only at a very advanced stage). Therefore, as a sensitivity analysis the Cox regression analyses were repeated, but with the follow-up period re-defined to exclude the first 14 days after first DC admission. All statistical analyses were conducted using R software for statistical computing (19).

RESULTS

First-time hospitalization for DC

During the period 1994-2013, a total of 1,169 HCV chronically-infected persons were hospitalized with first-time mention of DC (Table 1). The majority were males (74%) and the most frequent age-group was 40-49 years (39%). More than half (56%) had an alcohol-related admission prior to their first DC admission, and injecting drug use was indicated as the risk activity for acquiring HCV infection for 46% of the study population (85% of those with known risk). The number of new DC patients increased over time, from 63 (in the quinquennium 1994-1999) to 541 (in 2009-2013). Four percent were identified as HIV co-infected. The hierarchical classification of discharge diagnoses indicated that ascites was a more frequent complication (53%) than either hepatic failure or bleeding oesophageal varices. Fifty-four patients (5%) had a hospital admission with an HCC diagnosis code prior to their first DC admission (median of 124 days previously; IQR: 70-503 days).

Annual change in the number of first-time admissions for DC

The annual numbers of new DC patients, both overall and stratified by DC code category, is shown in Fig. 1a. The average annual percentage change in the numbers of DC patients by stratum of covariate is presented in Table 1. The average annual change in DC patient numbers increased over time, both overall (12.6% per year), and for all covariate strata**.** With respect to age, the largest average annual percentage change (15.9%) was observed for the 50-59 years age-group.

Outcomes following first-time admission for DC

Within the period 1 January 1994 through 31 May 2014, 722 and 95 DC patients died of a liver- or a non-liver related cause, respectively, and 106 DC patients had a subsequent first hospital admission for HCC. By the end of May 2014, 352 study cohort members were not known to have died. Median follow-up time for the mortality outcomes was 1.09 years (IQR: 0.22–3.47); for the outcome first subsequent HCC admission, median follow-up was 1.01 years (IQR: 0.18 –3.28), with

minimum and maximum follow-up times of 0 and 19.35 years. The cumulative annual number of patients with DC or with both DC and HCC and not known to have died, and the cumulative number of liver-related and non-liver related deaths, are shown in Fig. 1b.

The rates of liver-related and non-liver related mortality dropped rapidly over the initial 6 months following first DC admission (very high in the first two-week period) and then decreased more gradually with time since DC (Supporting Information, Table S1). Mortality rates for both endpoints were relatively stable over the four quinquennia of the study period (data not shown).

The annual transition probabilities between various disease states are shown in Fig. 2. The probability of a liver-related death following first DC admission was 20.9%, higher than the probability of either non-liver related death or first subsequent HCC admission (3.0% and 1.5% per year, respectively). Following the first subsequent HCC admission, the annual transition probabilities for liver-related and non-liver related mortality were 52.4% and 0%, respectively. Fig. 3 shows the proportion of the DC cohort in each disease state (the *state occupation probabilities*) over the first nine years of follow-up.

Survival analysis of time to outcome

Fig. 4 shows the cumulative risks of each of the four outcomes; the cumulative risks for the same four endpoints but stratified according to DC code category and according to the occurrence of at least one alcohol-related admission prior to first DC admission are provided in Supporting Information, Figs. S1 and S2. The five-year cumulative risks of liver-related mortality, all-cause mortality, non-liver-related mortality and first subsequent HCC admission were 61.3%, 69.5%, 8.2%, and 8.8%, respectively. If patients with an HCC admission prior to study entry are excluded,

the five-year cumulative risk of a first HCC admission decreases to 6.4%.

The results of the multifactorial Cox proportional hazards regression analyses of liver-related and all-cause mortality are presented in Table 2, with univariate Cox regression results in Supporting Information, Table S2. The relative risk of liver-related death among DC patients was significantly increased for males (HR=1.3, 95% CI: 1.1-1.6), current age 60+ years (HR=1.5, 95% CI: 1.2-2.0) compared with 40-49 years, and HCC hospital admission (HR=2.7, 95% CI: 2.2-3.4). There was a reduced relative risk for non-PWID risk for HCV acquisition (HR=0.7, 95% CI: 0.5-1.0) compared with PWID, a primary discharge diagnosis of bleeding varices (HR=0.7, 95% CI: 0.6-1.0), compared with hepatic failure, the occurrence of a post-liver transplant admission (HR=0.2, 95% CI: 0.1-0.3), and period of first DC admission 1994-1998 (HR=0.6, 95% CI: 0.5-0.9), compared with 1999-2003. The relative risk of all-cause mortality followed a very similar pattern, with comparable HR estimates (Table 2).

The frequency of the mortality outcomes investigated, when plotted as function of period of follow-up time (Supporting Information, Fig. S3) indicated a very high surge in events immediately following first DC admission. As a sensitivity analysis, we repeated the Cox regression analyses after excluding the first 14-days of follow-up. The resulting relative risk estimates were largely similar (see Supporting Information, Table S3).

For liver-related deaths only, the five most frequently occurring ICD codes in the underlying cause of death field were K70.9, B182, C220, K703, and K704 (*alcoholic liver disease, unspecified, chronic hepatitis C, liver cancer, cirrhosis, and alcoholic hepatic failure, respectively)*, which together accounted for 62% (445/ 722) of all liver-related deaths. For non-liver related deaths only, the five most

frequently occurring underlying cause of death ICD codes were R99, F112, F192, X42, and I189 (other ill-defined and unspecified causes of mortality, mental/behavioural disorders due to use of opioids, mental/behavioural disorders due to multiple drug use, accidental poisoning by and exposure to narcotics and psychodysleptics, other noninfective disorders of lymphatic vessels and lymph nodes, respectively), which together accounted for 41% (39/95) of the total.

DISCUSSION

Scotland has been experiencing an epidemic of HCV-related decompensated cirrhosis. During the last 20 years, we observed a nine-fold increase in new HCV-related DC patients between 1994 and 2013, with a corresponding rapid rise in the prevalent number of persons living with DC (Fig. 1). Besides the health burden of the disease itself, the financial burden to the Scottish health services for the management of chronic HCV-related severe disease will also have substantially increased. For example, based on estimated prices of managing DC and HCC (excluding liver transplantation costs)(20), the prevalent cohort of 379 chronic HCV patients with DC in 2013 (involving 109 patients also with HCC) would have cost the NHS around £6.4 million in 2013. When compared with the health care costs associated with the prevalent cohort of 20 patients with DC in 1996 (£305,000), this represents a 21-fold rise over a near 20-year period.

Over the 20-year study period, we found no evidence for improvement in the relative risks of liver-related or all-cause mortality associated with quinquennium of first DC hospitalization. Despite remarkable increases in rates of referral to tertiary care (i.e., specialist liver clinics) and of initiation on antiviral treatment among HCV patients in recent years in Scotland (13), mortality outcomes failed to show parallel improvements once the DC stage of liver disease had been reached. Moreover, the five-year cumulative incidence of all-cause mortality was notably high – at

70% – in this DC patient population, even though we lacked accurate data on liver transplantation. In a comparable period (1996-2014, mostly overlapping our study period), there were 176 first liver transplants in HCV infected persons in Scotland (12); a proportion of the observed extended survival in DC pts with liver failure (see Fig. 3) may be due to successful transplantation (we estimate 50% as an upper bound; 176 represents 50% of our cohort´s 5-year survivors). However, in multifactorial analyses we did adjust for an indicator of past liver transplantation, which was associated with a considerable reduction in mortality risk.

There have been few previous studies investigating the clinical course of disease in patients with HCV-related DC. In a cohort of 200 HCV-infected patients from two Barcelona liver clinics followed up for a mean of 2.8 years after their first hospital admission for DC, 17% developed HCC and all-cause mortality was 43% (21, 22). In a larger clinical cohort study involving 1,037 HCV infected/HIV-uninfected persons from eight Spanish hospitals followed up for a median 13 months, 37% of patients died, of which 86% was due to a liver-related cause (23). There is uncertainty, however, in generalising findings based on primarily academic research centre clinical populations, which may be subject to selection bias, to the wider DC patient population. For instance, five-year survival in DC patients reported for an HCV patient cohort (21) was notably better: 51% compared with 30% for our cohort; for comparison, the 5-year cumulative mortality incidence from a systematic review of disease progression in cirrhotic patients (not only due to HCV infection) is roughly 75% (24). Our estimate of the annual transition probability of death following DC (24%; summing liver-related and non-liver related causes) is also much higher than the pooled estimate of 14.5% arrived at via meta-analysis of three clinical cohorts (1, 2, 3, 25).

Development of HCC or death following DC may be influenced by underlying co-morbidities (26).

For instance, our study population had a high baseline rate (56%) of prior hospitalization for an alcohol-related cause, which we included as an (imperfect) proxy for problem alcohol use. However, we found no evidence for an effect of alcohol-related hospitalization (proxy for problem alcohol use) on the relative risk of death, after adjusting for other covariates. Although Scotland's HCV-diagnosed population has a high prevalence of problem alcohol use, alcohol-related liver disease as a co-morbid condition is also characteristic of other, mainly substance-abusing, HCV-infected populations (26, 27) We emphasise the importance of quantifying the benefit of treatment with the new DAAs among all DC patients – including those with extensive co-morbidities – in terms of survival, and not just a sustained virological response (28). Record-linkage methods similar to those described here may prove useful for establishing the prognosis of patients treated with DAAs and attaining SVR post-DC diagnosis.

Despite the power and large sample size afforded by our record-linkage study design (analysis of our nationwide cohort – comprised of patients from approximately 200 hospitals – largely overcomes the above-mentioned limitation inherent with study populations of patients attending tertiary care clinics), we note the existence of several limitations. First, we lacked data informing liver disease prognosis, such as provided by a Child-Pugh or MELD score.

Second, our information on HIV co-infection, which has been associated with an increased relative risk of mortality in DC patients (reported hazard ratio of 2.3 (23)), may have been impoverished as it was derived from hospitalization history. However, the percentage of HIV co-infected DC patients (4.4%) is comparable to that reported in the previous Scottish study (9) that employed record-linkage to the national HIV register, which found 2.3% of the HCV-diagnosed study population to be HIV co-infected.

Third, we defined the covariate alcohol-related hospitalization to serve as a proxy for problem alcohol use, as no quantitative data on alcohol consumption by our study population were available. This measure is only a crude indicator of problem alcohol use (although alcohol-related admission rates have been shown to correlate with self-reported intake; (29)). This suggests a reason for the observed lack of association of this covariate with mortality in multifactorial analysis.

Our study inclusion criteria required a first hospital admission for DC. Record-linkage to hospital inpatient data should have high sensitivity as almost all DC patients will be admitted to hospital. However, an unknown number of persons developing DC and who were not admitted to hospital will have been excluded. This number is likely to be very small given that in the previous Scottish record-linkage analysis of HCV-diagnosed patients developing DC in the period 1996-2006 (9), only 6% (63/1058) of those patients who had died with mention of DC in their death record had not been previously admitted to hospital. Finally, we have not been able to follow-up those DC patients who were hospitalized or who had died outwith Scotland, although these numbers are anticipated to be small.

Conclusions

Over the last 20 years, there has been no observable improvement in severe outcomes among HCV chronically-infected patients in Scotland who have developed decompensated cirrhosis. The annual numbers of incident and prevalent DC cases showed a rising trend, and the relative risks of all-cause and liver-related death did not vary over the study period. The present results are important for establishing the expected risks of severe disease outcomes among DC patients in the

interferon-based treatment era, and will be useful for calibrating and/or validating HCV disease projection and health economic models (30-32). Further monitoring of the numbers of incident and prevalent DC cases, and the risks of death and complications among persons with DC, is of utmost importance in the era of new DAA treatments.

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STATEMENT OF INTERESTS

HAI reports personal fees from Janssen and speaker fees from Gilead, outside the submitted work. SJH has received honoraria for presenting at meetings/conferences from Abbvie, Gilead, Janssen, MSD, Roche.

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SUPPLEMENTARY MATERIAL

Document file: *Supporting_Information_McDonald_JVH.pdf*

Table 1. Baseline characteristics of HCV chronically-infected patients with decompensated cirrhosis (DC).

Factor	Level	N	(%)	Annual % change**
Sex	Males	862	(73.7)	12.3
	Females	306	(26.2)	13.5
	NK	1	(0.1)	–
Age at first DC hospital admission (years)	<40	304	(26.0)	10.2
	40-49	451	(38.6)	13.4
	50-59	278	(23.8)	15.9
	60+	136	(11.6)	10.1
Year of first DC admission	1994-1998	63	(5.4)	–
	1999-2003	200	(17.1)	–
	2004-2008	365	(31.2)	–
	2009-2013	541	(46.3)	–
≥1 Alcohol-related admission prior to first DC admission	Yes	650	(55.6)	13.8
	No	519	(44.4)	11.3
Risk group	PWID (ever)	532	(45.5)	14.5
	Non-PWID	96	(8.2)	12.0
	Not known	541	(46.3)	7.1
DC diagnosis code category*	Hepatic failure	419	(35.8)	12.0
	Ascites	614	(52.5)	14.1
	Bleeding varices	135	(11.6)	8.6
HIV code in any admission	Yes	51	(4.4)	6.2
	No	1118	(95.6)	13.0

≥1 admission for HCC prior to first DC admission	Yes	54	(4.6)	20.9
	No	1115	(95.4)	12.3
Time since HCV diagnosis date (years)	-1 to 0 years since HCV	146	(12.5)	6.2
	0 to <1 year since HCV	207	(17.7)	7.5
	1 to <3 years	194	(16.6)	8.9
	3 to <5 years	149	(12.7)	10.2
	5 to <10 years	268	(22.9)	16.1
	10+ years	205	(17.5)	32.6

Note: Study population is defined as first hospital admission with mention of DC occurring within the period 1994-2013 (n = 1,169). The average annual percent change over the study period in the number of DC patients is also shown (12.6% overall).

PWID = people who inject drugs; HCC = hepatocellular carcinoma.

* Because more than one code category can appear in the hospital episode record of an individual patient, a hierarchical definition was used; e.g., if a hepatic failure code occurs in one of six possible diagnosis fields: DIAG1 (primary diagnosis) through DIAG6 (supplementary diagnoses), the patient will be counted as such, even if one or more of the other code categories also occurred in the hospital record. If no hepatic failure code but an ascites code occurs in any of the diagnosis fields, then category 'ascites' is assigned, and so forth.

** P-values for annual percentage change are all < 0.01, except for ´HIV code in any admission=yes´ (P=0.0169).

Table 2. Results of multifactorial Cox proportional hazards regression analysis of patient and other characteristics on various endpoints (1994 to 31 May 2014) in HCV chronically-infected DC patients.

Risk	Liver-related death (*n*=722)				All-cause death (*n*=817)			
Factor	*n*	pyrs	HR	95% CI	*n*	pyrs	HR	95% CI
Sex F	167	857		Ref.	191	857		Ref.
M	555	2133	**1.30**	**1.09-1.55**	626	2133	**1.28**	**1.09-1.52**
Current age (years)								
<40	132	621	0.97	0.78-1.20	152	621	0.94	0.77-1.14
40-49	266	1155		Ref.	311	1155		Ref.
50-59	200	811	1.02	0.84-1.23	219	811	0.99	0.83-1.19
60+	124	402	**1.53**	**1.20-1.95**	135	402	**1.52**	**1.21-1.91**
Alcohol-related hospitalization								
No	185	798		Ref.	207	798		Ref.
Yes	537	2191	1.07	0.89-1.28	610	2191	1.05	0.88-1.25
Period of first DC hospital admission								
1994-98	42	384	**0.64**	**0.46-0.91**	52	384	**0.70**	**0.51-0.96**
1999-03	145	802		Ref.	167	802		Ref.
2004-08	262	1031	1.08	0.88-1.33	292	1031	1.06	0.87-1.29
2009-13	273	773	1.06	0.86-1.31	306	773	1.06	0.87-1.29
Risk group for acquisition of HCV infection								
PWID	307	1326		Ref.	365	1326		Ref.
NonPWID	54	360	**0.72**	**0.53-0.98**	62	360	**0.70**	**0.53-0.93**
NK	361	1304	1.15	0.97-1.37	390	1304	1.07	0.91-1.26
DC code category								
Hepat. failure	265	1044		Ref.	298	1044		Ref.
Ascites	377	1512	0.91	0.77-1.06	428	1512	0.93	0.80-1.08
Varices	80	434	**0.74**	**0.58-0.96**	91	434	**0.76**	**0.60-0.97**
HCC admission prior to first DC admission								
No	618	2822		Ref.	713	2822		Ref.

Yes	104	168	**2.71**	**2.15-3.42**	104	168	**2.50**	**1.99-3.14**	
HIV co-infection									
No	689	2886		Ref.	775	2886		Ref.	. .
Yes	33	104	1.42	0.99-2.04	42	104	**1.57**	**1.13-2.16**	
Post-liver transplantation admission									
No	698	2653		Ref.	793	2653		Ref.	. .
Yes	24	337	**0.22**	**0.14-0.34**	24	337	**0.20**	**0.13-0.31**	

Note. Study population defined as patients with first DC hospital admission in period 1994–2013; n=1,169. Current age, alcohol-related hospitalization, admission for HCC, and post-liver transplantation admission are coded as time-dependent covariates. Boldface indicates conventional statistical significance.
NK = not known; PWID = people who inject drugs; HCC = hepatocellular carcinoma.

FIGURE LEGENDS

Fig. 1. Annual numbers of first DC hospital admissions (panel **A**) and cumulative annual numbers of deceased and living DC patients (**B**), over the period 1994–2013.

Fig. 2. Annual transition probabilities of various outcomes following first hospital admission with DC among persons chronically-infected with HCV in Scotland (study period 1 January 1994 to 31 May 2014). Values are averages of the individual transition probabilities for the first three years of follow-up. Annual mortality probabilities within square brackets are calculated with the first 14 days of follow-up excluded.

Fig. 3. Proportion of DC patient cohort as a function of time since first DC admission occupying the following disease states: decompensated cirrhosis (alive), HCC (alive), dead following HCC, and dead without HCC. The area shaded black represents the proportion of the DC patient cohort living with HCC.

Fig. 4. Cumulative risk of four specified endpoints among DC patients (defined as HCV chronically-infected persons who had their first DC hospital admission in the period 1994–2013) following first DC admission: for liver-related death (**A**), all-cause death (**B**), first HCC hospital admission (**C**), and non-liver related death (**D**). Follow-up time in each plot is censored on the last day of study period (31 May 2014).